REMARKS

Justification for the amendments is as follows. Claim 1 has been amended to delete the terms "portion thereof", "oligopeptide" and "biologically active portion". Claims 1 and 2 have been amended to delete SEQ ID NO:2 and to limit the claims to polynucleotides encoding SEQ ID NO:1, and fragments and variants thereof. Claim 3 has been amended to recite a further limitation of claim 1, e.g., SEQ ID NO:3, a polynucleotide encoding SEQ ID NO:1, and specific fragments and variants of said sequence. Support for the specific fragments recited in claim 3 is found in the specification at p. 11, lines 30-31. Since claim 3, as amended, falls within the scope of the elected claims of Group I as defined by the Examiner in the Restriction Rquirement (Paper No. 4), Applicants therefore request rejoining of claim 3 with the elected group. Claim 4 has been amended to correct antecedant basis for the term "composition" in the claim, and claim 5 has been canceled. New claim 21 has been added to further limit the method of claim 11. Support for new claim 21 is found in the specification, for example, at pp. 10-11 which describes substrates used for the attachment of cDNA probes. No new matter is added by any of these amendments, and entry of the amendments is respectfully requested.

35 USC § 112, First Paragraph, Rejection of Claims 1(e) and 5

The Examiner has rejected claims 1(e) and 5 under 35 USC § 112, first paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner stated that claim 1(e) recites "biologically active " portion but that the disclosure does not teach the metes and bounds for activity. Applicants have deleted the term "biologically active portion" from the claim.

The Examiner also stated that claim 5 recites "substrate" but that it is not clear as to what substrate comprises the claimed cDNA. Applicants disagree that the term "substrate" as recited in the claim is unclear. The term "substrate" as used for the attachment of cDNA probes in, for example, a microarray is clearly defined at p. 10 line 31 through p. 11, line 2. However, in the interest of expiditing the allowance of claims, applicants have canceled claim 5 and substituted new claim 21 to recite a method of using a cDNA probe attached to a substrate.

With these amendments and arguments, Applicants believe claim 1 is clear and definite and respectfully request the withdrawal of the rejection of claims under 35 USC § 112, first paragraph.

35 USC § 112, First Paragraph, Rejection of Claims 1-2 and 4-8

The Examiner has rejected claims 1-2 and 4-8 under 35 USC § 112, first paragraph, as containing subject matter which is not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner stated that the instant disclosure fails to meet the enablement requirement for the following reasons:

5. The specification discloses that the claimed cDNA may be used to diagnose colon cancer [because the claimed cDNA] shows differential expression in colon cancer tissue versus normal colon tissue. Since there is no evidence in the art or in the specification teaching SEQ ID NO:1 expression levels and its correlation with colon cancer, it would be unpredictable to use it to diagnose cancer based on SEQ ID NO:1 expression. Furthermore, in order for the claimed invention to be used to diagnose colon cancer it must be certain that changes in the expression levels of SEQ ID NO:1 in a normal biological sample as compared to levels in a cancerous biological sample is indicative of a cancer and not some other disease.

Applicants submit that evidence teaching SEQ ID NO:1 expression levels and its correlation with colon cancer is provided in the specification, specifically in the data presented in Tables 2 and 5. In support of this, Applicants submit a Declaration under 37 CFR 1.132 of Dr. Amy Lasek, an inventor on the application. In her declaration, Dr. Lasek explains how one skilled in the art would readily be able to use the claimed polynucleotides in the diagnosis of colon cancer, or in monitoring the treatment of a colon cancer, using the information provided in the specification. In particular, Dr. Lasek points out that presenting the results of microarray experiments comparing expression levels of a gene in a diseased state, such as colon cancer, with levels in normal tissue as a ratio of the two expression levels, is common in the art. One skilled in the art would readily be able to use this information to compare the level of SEQ ID NO:1 expression in, for example, biopsied normal tissue from a patient with suspected colon cancer, with that in the suspected tumor tissue from the same patient to provide a diagnosis. Dr. Lasek also testifies in her declaration that the data from both Tables 2 and 5 show that the expected differential expression between normal colon tissue and cancerous colon tissue in a given individual would be at least a 2-fold decrease in the cancerous tissue. With respect to the Examiner's allegation that there would be no certainty that the differential expression of SEQ ID NO:1 in a suspected cancerous biological sample is not indicative of some other disease, Applicants submit that, as testified by Dr. Lasek in her declaration, an initial diagnosis of a suspected colon cancer would likely be made on some other criteria such as tissue

pathological examination, that would likely rule out other diseased conditions such as, for example, ulcerative colitis. Thus the differential expression of SEQ ID NO:1 in other diseased colon conditions would not likely be an issue in the diagnosis. Furthermore, it would clearly not be an issue in the disclosed use of the polynucleotide to monitor therapeutic intervention in an established colon cancer (see specification, at p. 21, lines 9-11).

The Examiner further stated that it would require undue experimentation to one of ordinary skill in the art to make an antigenic epitope, oligopeptide, biologically active portion of SEQ ID NO:1 or 2 because there is no guidance as to which regions of the cDNA may be used to make an epitope or oligopeptide that will function as contemplated.

Applicants have deleted the terms "oligopeptide" and "biologically active portion" from the claims. With respect to the identification of an antigenic epitope of SEQ ID NO:1 or 2, the specification clearly teaches well known methods in the art to identify suitable antigenic epitopes of SEQ ID NO:1 or 2, as well as providing specific examples of such epitopes. For example; "an antigenic epitope of the protein identified using Kyle-Doolittle algorthims of the PROTEAN program (DNASTAR, Madison WI"(p. 10, lines 9-10); "the amino acid sequence of IP is analyzed using LASERGENE software (DNASTAR) to determine regions of high antigenicity; "An antigenic epitope, usually found near the C-terminus or in a hydrophilic region is selected---. Typically, epitopes of about 15 residues in length are produced---" (p. 40, lines 17-20); and "Useful antigenic epitopes [of SEQ ID NO:1] extend from T66 to H90, L120 to R141, D234 to R245, and I351 to N359" (p. 12, lines 13-15), "Useful antigenic epitopes [of SEQ ID NO:2] extend from T104 to R140 and R194 to K206" (p. 13, line 13). Applicants therefore submit that it would not require undue experimentation on the part of one skilled in the art to identify the claimed epitopes of SEQ ID NO:1 and 2.

6. The specification discloses the differential expresion of SEQ ID NO:1 in colon cancer tisssue versus normal colon tissue (Table 5) using microrray analysis, but does not provide guidance as to what level of expression would constitute abnormal levels and how these levels would be indicative of colon cancer. The disclosure only shows the detection of SEQ ID NO:1 expression in known cancers and does not give any definitive evidence of cancer diagnosis. Accordingly, one of ordinary skill in the art would be required to perform undue experimentation in order to practice the invention as claimed.

The Examiner appears to require that applicants submit results of a clinical study to satisfy the enablement requirement of 35 USC § 112, first paragraph. There is not, and never has been, such a requirement by the PTO to satisfy the patentability requirements under this pargraph. The courts have

repeatedly held that all that is required for therapeutic use of a biological agent is a "reasonable correlation" between activity and the asserted use. Nelson v. Bowler, 626 F.2d 853, 857, 206 USPQ 881, 884 (CCPA 1980). In the instant case a "reasonable correlation" between SEQ ID NO:1 expression and colon cancer for diagnostic pruposes is evidenced by data showing at least a two-fold reduction of SEQ ID NO:1 in colon cancer compared to normal colon tissue, enabling one of ordinary skill in the art to use this information in the diagnosis of colon cancer as described above and in the declaration of Dr. Lasek without undue further experimentation. Applicants need only prove a "substantial likelihood" of utility, and hence of enablement; certainty is not required. *Brenner v. Manson*, 383 U.S. 519, 532, 148 USPQ 689 (1966). It is the burden of the Examiner to prove otherwise, and the Examiner has presented no such evidence. The M.P.E.P. further elaborates on the burden of the Examiner to establish a proper *prima facie* case for nonenablement in ¶ 2164.04:

> the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).---it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in the supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement---. 439 F.2d at 224, 169 USPQ at 370.

The Examiner has presented no such evidence or reasoning to contest Applicants assertion that the claimed invention is useful for, and enabled by the specification in, the diagnosis of a colon cancer based on the differential expression data provided in Tables 2 and 5 particularly when used, as is common in the art, in conjunction with other diagnostic indicators. The Examiner has merely asserted that Applicants have not given any definitive evidence of cancer disgnosis.

7. The Examiner stated that the general state of the art and level of predictability of hybridization technology is taught by Lehninger et al. (Principles of Biochemistry, 2nd Ed., Worth Publishers, NY, 1993), which teaches that complementary strands are not identical in either base pair sequence or composition, and that Applicant has not taught how to hybridize identical nucleic strands one to another and, in view of Lehninger et al., one of ordinary skill in the art would not clearly expect to be able to hybridize two identical nucleic acid strands to one another.

Applicants are not clear as to exactly what claims the Examiner is referring to in making a rejection based on the above statements. Applicants are well aware of the definition and use of the term

"complementary" in hybridization studies as evidenced by the definition of the term the "complement" of a cDNA provided at p. 8 of the specification. Applicants do not teach anywhere in the specification or claims the hybridization of identical nucleic acid strands with one another. Reference to a "cDNA or the complement" of a cDNA, as recited in claims 4 and 6, reflects the well known fact that a naturally occurring RNA or DNA sequence corresponding to the claimed cDNA seqeuence of the invention may exist in a biological sample as either the identical sequence or the "complementary" sequence, and therefore that either strand, the "positive" or "negative"(e.g., complementary) strand may be used as a probe in hybridization studies.

8. With regard to variants of polynucleotides encoding SEQ ID NO:1, as recited in claim 1, The Examiner stated that there are many nucleic acid molecules that may or may not perform the same biological functions and the specification does not give any guidance to which molecules having at least 80% sequence identity to SEQ ID NO:1 will exhibit the biological activities as the claimed, or any guidance as to which regions of amino acid sequence are responsible for biological activity, as biological activity is not taught and thus, must be preserved so the molecule will function as claimed.

Biological activity has not been recited or claimed as the primary basis for the utility, or enablement for the claimed polynucleotides encoding SEQ ID NO:1 or its variant sequences. Rather the specification discloses at p. 14, lines 34-36 (as amended) that "The cDNA and fragments or variants thereof (SEQ ID NOs:3-29) may be used in hybridization, amplification, and screening technologies to identify and distinguish among SEQ ID NO:1, SEQ ID NO:2, and related molecules". There is therefore no need for one to assay the claimed sequences for any particular biological activity in order to use them as disclosed in the specification. Applicants would be more than willing, however, to limit the claimed variant sequences to the specific sequences, SEQ ID NOs:16, 17-18, 19-22, and 23-29 disclosed in the Table at p. 14, and as originally claimed in claim 3, however, the Examiner has refused to examine these sequences as constituting an undue burden of search.

9. The Examiner stated that protein chemistry is one of the most unpredictable areas of biotechnology and citing Burgess et al. (1990) and Lazar et al. (1998) with respect to the potential effect of even a single amino acid change on the biological activity of a protein. The Examiner further cited Bowie et al. (1990) with respect to the unpredictability of amino acid substitution on three-dimensional structure/function relationships in a protein. The Examiner concluded that in view of this unpredictability, one skilled in the art would require undue experimentation to practice the invention as claimed.

Applicants presume that these comments are directed to the claimed variant sequences of the

polynucleotide encoding SEQ ID NO:1, an again point out that biological activity is not at issue in the use of these sequences. Applicants further point out that as defined at p. 11, lines 3-9 of the specification, "variant" sequences as claimed in the instant invention refer to naturally-occurring polynucleotide and proteins subject to the laws of nature, and of evolutionary conservation in particular. In contrast, Lazar and Burgess, cited by the Examiner, are laboratory studies in which deliberate site-directed mutagenesis was used to artificially create deactivated proteins. In both of these cases, particular amino acid residues with known importance to protein function were specifically targeted for site-directed mutagenesis. Such artificial mutations created in the laboratory are not analogous to the naturally-occcurring variants as claimed, which are profoundly influenced by natural selection to conserve function. Bowie et al., also cited by the Examiner further supports this position. As stated by the Examiner, Bowie et al. specifically states that residues that are directly involved in protein functions such as binding will certainly be among the most conserved (emphasis added). Therefore, the likelihood that one of skill in the art would routinely expect to find seemingly inconsequential amino acid substitutions that dramatically affect the function or biological activity of naturally-occurring variants of a particular protein, such as that claimed, is unsubstantiated by the Examiner's evidence, and would not necessitate undue experimentation to identify them.

For all the above reasons, Applicants believe the claims, as amended, are fully enabled by the specification and respectfully request withdrawal of the rejection of claims 1-2 and 4-8 under 35 USC § 112, first paragraph.

35 USC § 102(b), Rejection of Claims 1-2 and 4-8

The Examiner has rejected claims 1-2 and 4-8 under 35 USC § 102(b) as anticipated by Bool et al. (1993). The Examiner stated that Boll et al. teach a portion of SEQ ID NO:1 as recited in claim 1, and therefore anticipates the claimed invention. Applicants have deleted the phrases "a portion thereof" or "a fragment thereof" from the claims and respectfully request withdrawal of the rejection of these claims as anticipated by Boll et al.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Agent at (650) 845-5741.

Please charge Deposit Account No. **09-0108** in the amount of $110.00 as set forth in the enclosed fee transmittal letter. If the USPTO determines that an additional fee is necessary, please charge any required fee to Deposit Account No. **09-0108.**

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION

The paragraph beginning at page 13, line 25 has been amended as follows:

Mammalian variants of the cDNA encoding IP-1 or IP-2 were identified using BLAST2 with default parameters and the ZOOSEQ databases (Incyte Genomics). These preferred variants have from about 80% to about 100% identity as shown in the table below. The first column shows the SEQ ID for the protein encoded by the human cDNA (SEQ ID_H); the second column, the SEQ ID for the variant cDNAs (SEQ ID_{var}); the third column, the clone number for the variant cDNAs ($Clone_{var}$); the fourth column, the library name; the fifth column, the alignment of the variant cDNA to the human cDNA (includes the alignment of different regions of the variant cDNA with different regions of the human cDNA in some cases); and the sixth column, the percent identity to the human cDNA.

The paragraph beginning at page 14, line 34 has been amended as follows:

The cDNA and fragments and variants thereof (SEQ ID NOs:3-29) may be used in hybridization, amplification, and screening technologies to identify and distinguish among SEQ ID NO:1, SEQ ID NO:2, and related molecules in a sample. The mammalian cDNAs may be used to produce transgenic cell lines or organisms which are model systems for human colon disorders, particularly colon cancer, Crohn's disease, and ulcerative colitis and upon which the toxicity and efficacy of potential therapeutic treatments may be tested. Toxicology studies, clinical trials, and subject/patient treatment profiles may be performed and monitored using the cDNAs, proteins, antibodies and molecules and compounds identified using the cDNAs and proteins of the present invention.

IN THE CLAIMS:

Claim 5 has been canceled.

Claims 1- 4 have been amended as follows:

1. (Once Amended) An isolated mammalian cDNA [or a fragment thereof] encoding a mammalian protein [or a portion thereof] selected from:

a) an amino acid sequence of SEQ ID NO:1 [and SEQ ID NO:2];

b) a variant having at least 80% identity to the amino acid sequence of SEQ ID NO:1 [or SEQ ID NO:2]; and

c) an antigenic epitope of SEQ ID NO:1 [or SEQ ID NO:2;

d) an oligopeptide of SEQ ID NO:1 or SEQ ID NO:2; and

e) a biologically active portion of SEQ ID NO:1 or SEQ ID NO:2].

2. (Once Amended) An isolated mammalian cDNA encoding a mammalian protein of SEQ ID NO:1 [or SEQ ID NO:2].

3. (Twice Amended) An isolated mammalian cDNA or the complement thereof selected from:

a) a nucleic acid sequence of SEQ ID NO:3 [and SEQ ID NO:10];

b) a fragment of SEQ ID NO:3 [selected] from about nucleotide 170 to about nucleotide 220, from about nucleotide 1015 to about nucleotide 1055, or from nucleotide 1500 to 1550 of SEQ ID NO:3; and [SEQ ID NOs:4-9;]

c) [a fragment of SEQ ID NO:10 selected from SEQ ID NOs:11-15; and

d)] a variant of SEQ ID NO: 3 [or SEQ ID NO:10 selected from SEQ ID NOs:16-29 and] having at least 80% identity to the nucleic acid sequence[s] of SEQ ID NO:3 [or SEQ ID NO:10].

4. (Once Amended) A [The] composition comprising the cDNA or the complement of the cDNA of claim 1.